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FIG. 1

The Enterohepatic Circulation with Key Transporter Proteins Mediating Bile Acid Circulation

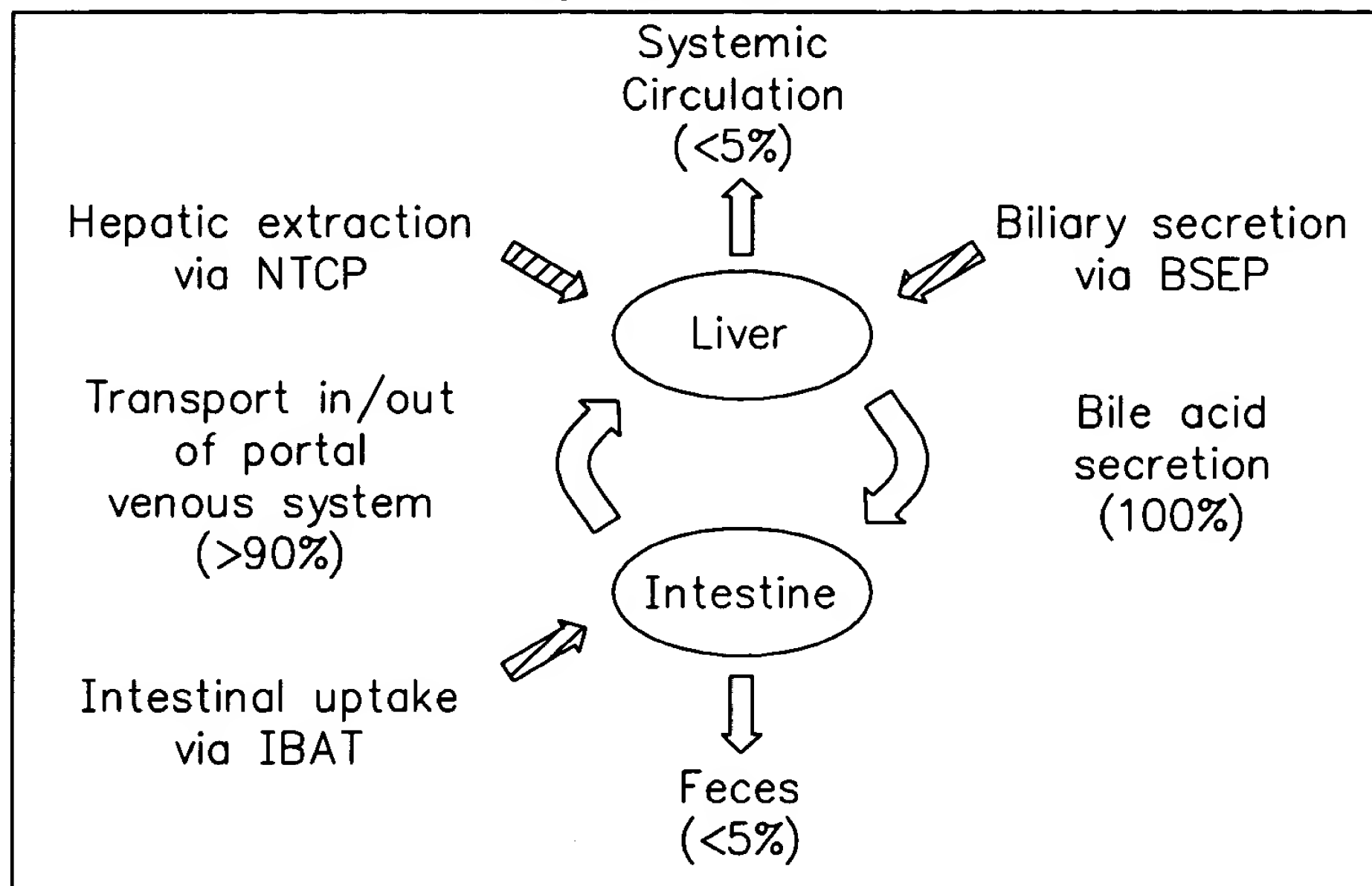
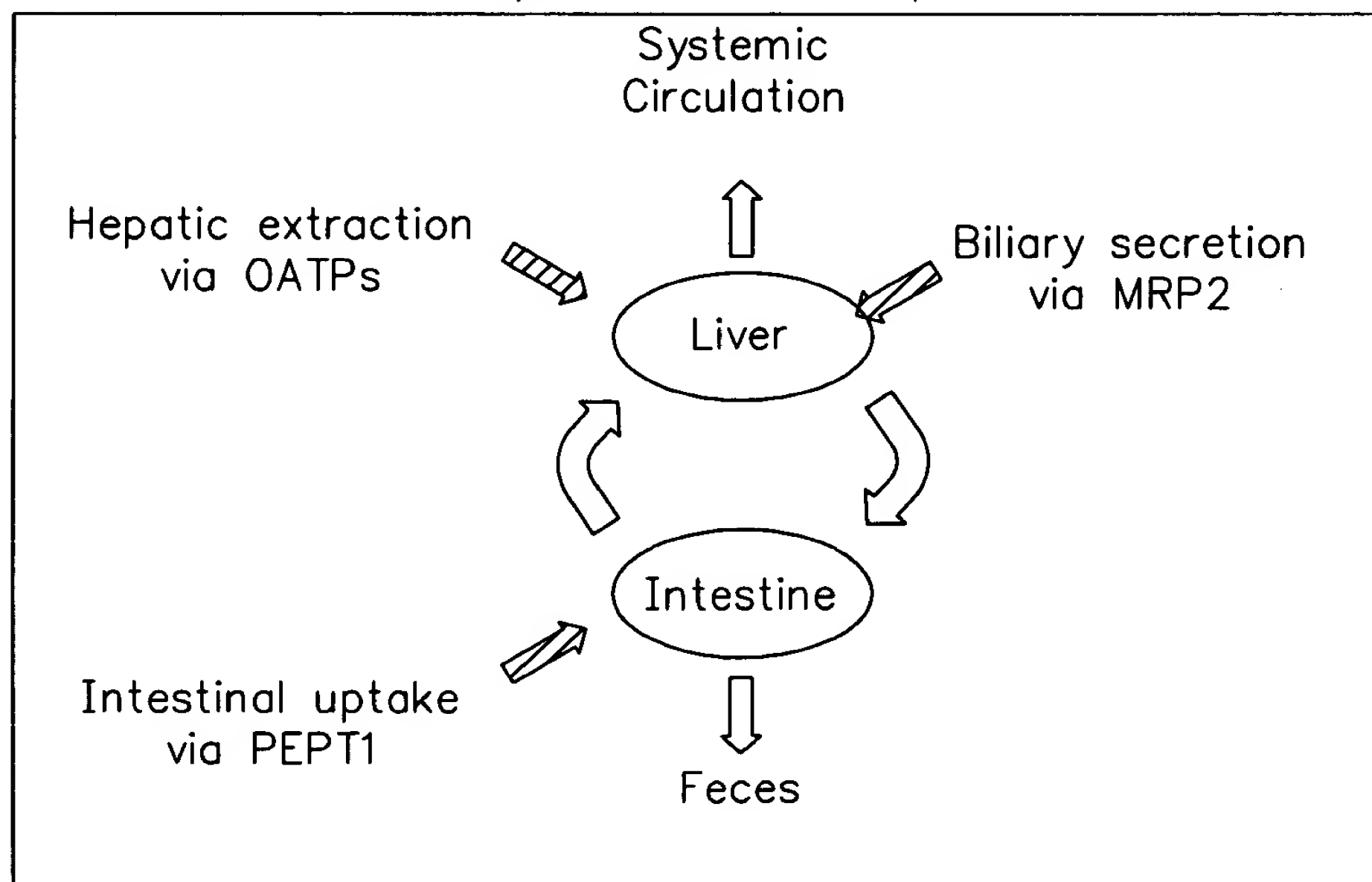


FIG. 8

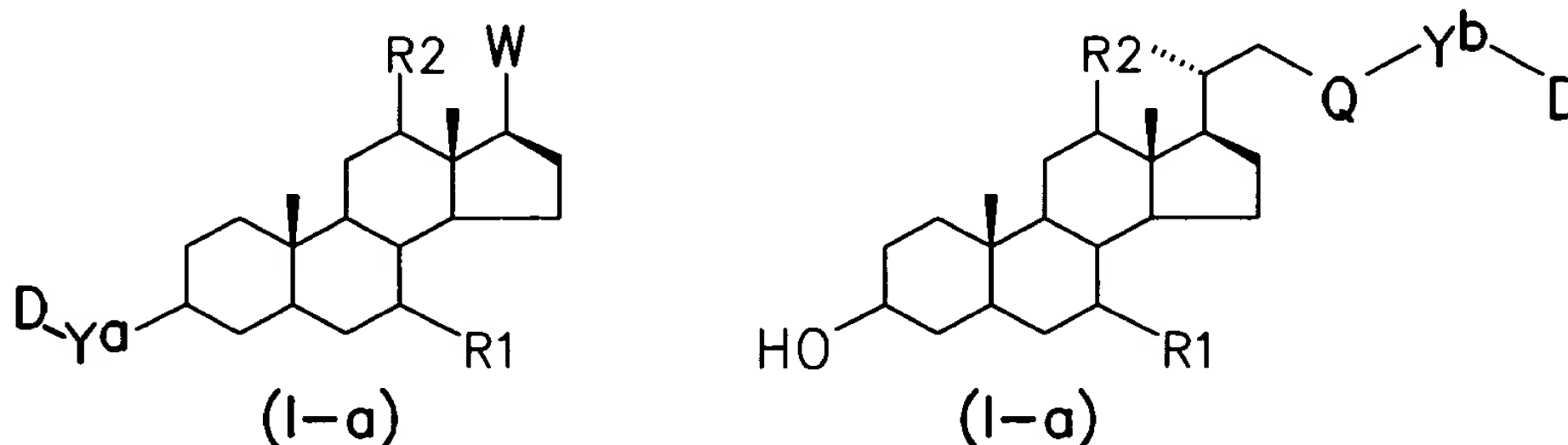
Enterohepatic Circulation Mediated by Intestinal Peptide and Hepatic Anion Transporters



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FIG. 2

Bile Acid Prodrug Derivatives for Sustained Release of Drugs



γ^a , γ^b are cleavable linker groups

D is a drug moiety

Q is CH_2 or O

W is selected from the group consisting of $-\text{CH}(\text{CH}_3)\text{W}'$ where W' is a substituted alkyl group containing a moiety which is negatively charged at physiological pH, which moiety is selected from the group consisting of $-\text{COOH}$, $-\text{SO}_3\text{H}$, $-\text{SO}_2\text{H}$, $-\text{P}(\text{O})(\text{OR}^6)(\text{OH})$, $-\text{OP}(\text{O})(\text{OR}^6)(\text{OH})$, $-\text{OSO}_3\text{H}$ and pharmaceutically acceptable salts thereof

$\text{R}_1 = \text{R}_2 = \alpha\text{-OH}$ (from Cholate)

$\text{R}_1 = \alpha\text{-OH}$, $\text{R}_2 = \text{H}$ (from Chenodeoxycholate)

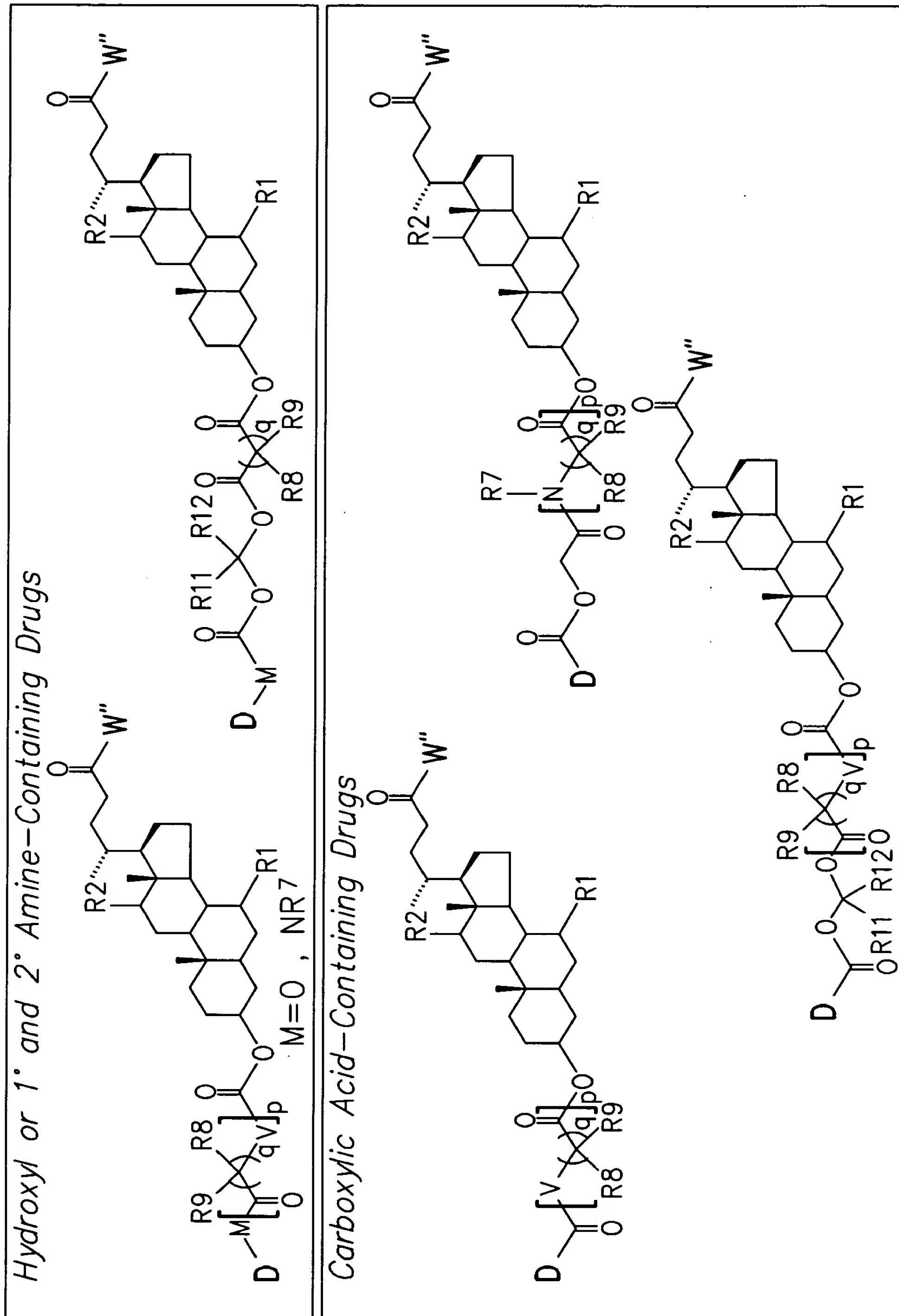
$\text{R}_1 = \beta\text{-OH}$, $\text{R}_2 = \text{H}$ (from Ursodeoxycholate)

$\text{R}_1 = \text{H}$, $\text{R}_2 = \alpha\text{-OH}$ (from Deoxycholate)

$\text{R}_1 = \beta\text{-OH}$, $\text{R}_2 = \alpha\text{-OH}$ (from Ursocholate)

$\text{R}_1 = \text{R}_2 = \text{H}$ (from Lithocholate)

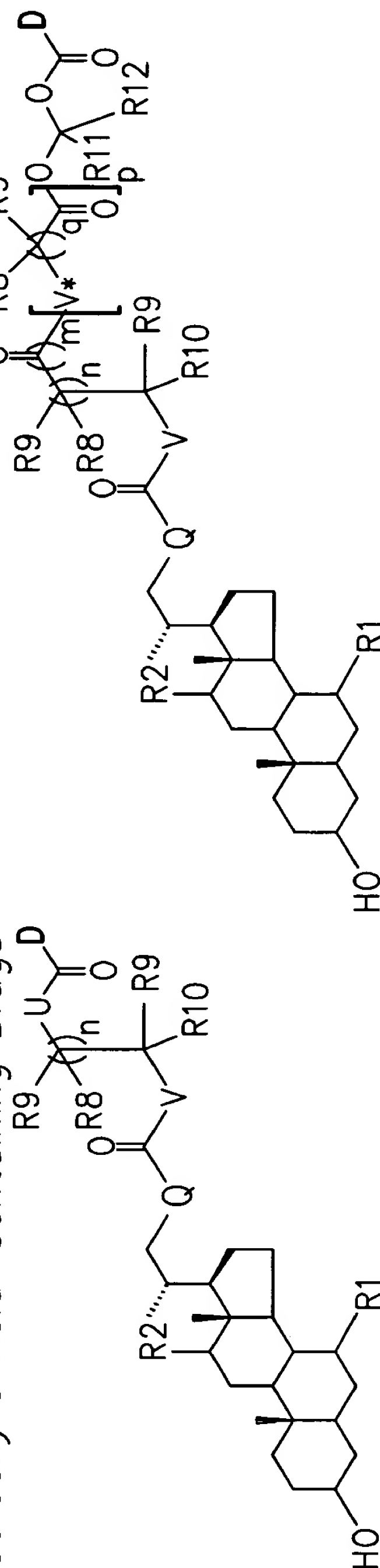
FIG. 3 Generic Structures of Preferred Bile Acid C-3 Derivatives



W''' is OH, NHCH₂CO₂H, NHCH₂CH₂SO₃H or pharmaceutically acceptable salts thereof

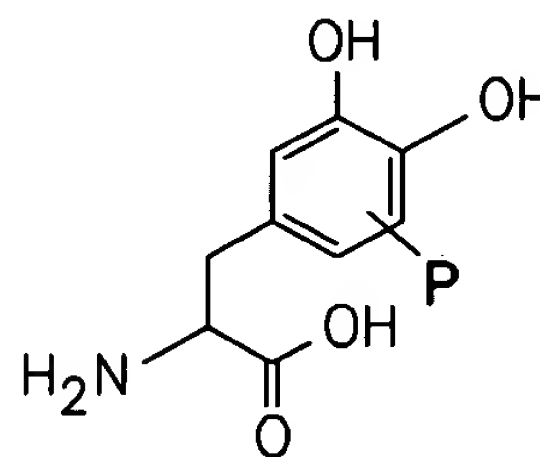
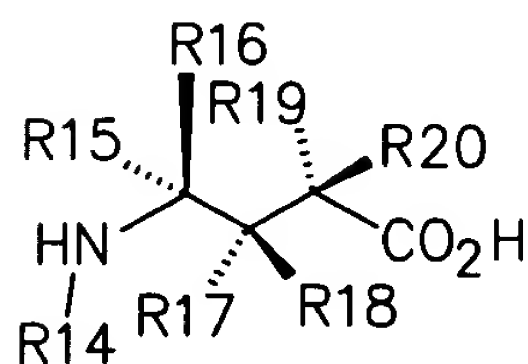
Hydroxyl or 1° and 2° Amine-Containing Drugs





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FIG. 5

GABA Analog Derivatives and L-Dopa Derivatives



Generalized GABA Analog

Optionally Protected L-Dopa Analog

R14, R15, R16, R19 and R20 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl and substituted heteroarylalkyl;

R17 and R18 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, acyl, substituted acyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl and substituted heteroarylalkyl or optionally, R17 and R18 together with the carbon atom to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl or bridged cycloalkyl ring;

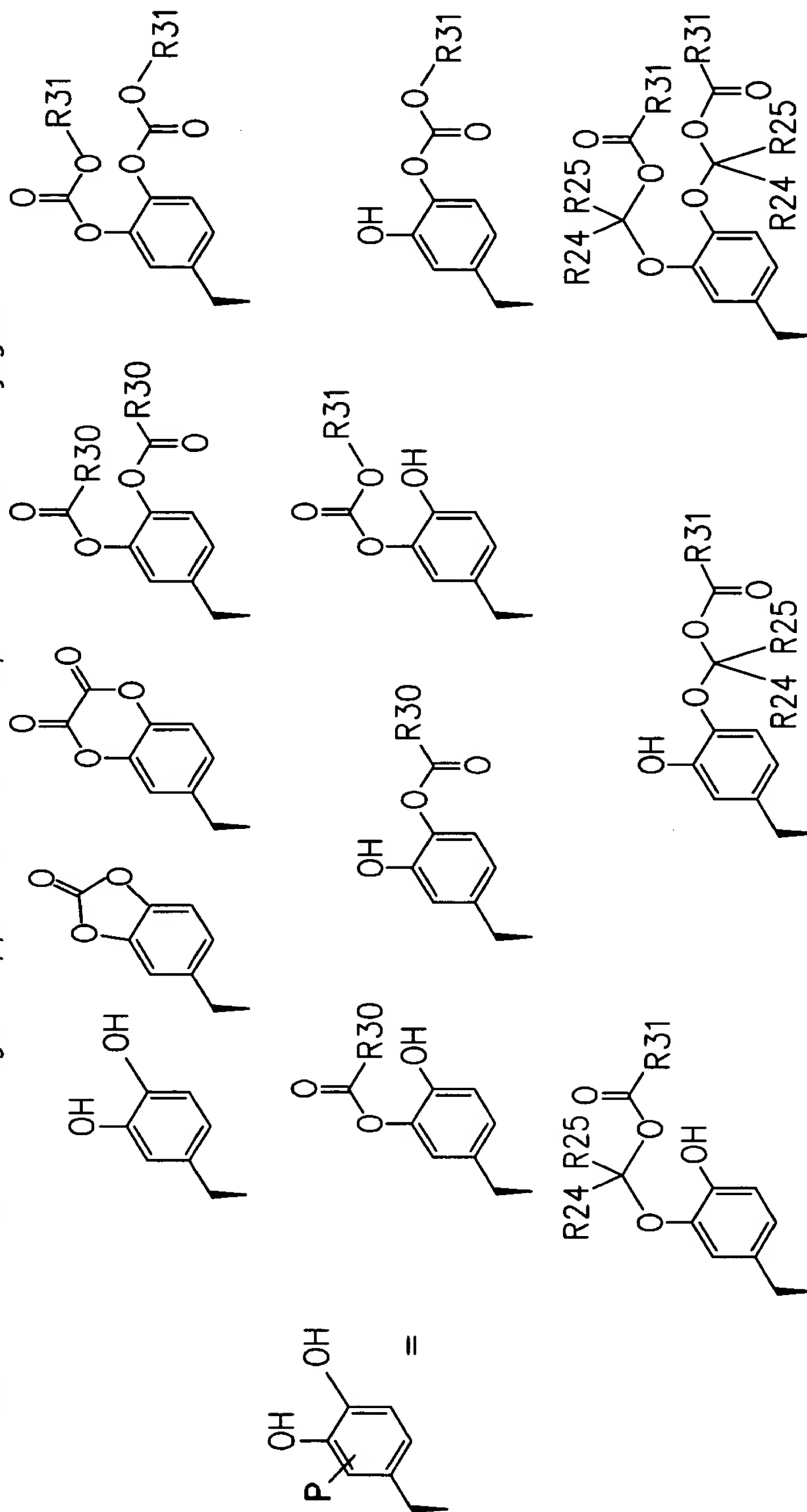
P is a catechol protecting group (see Figure 6)

The GABA analog or L-Dopa analog is attached to the steroid nucleus in (I-a) or (I-b) either by replacement of one of the amino hydrogen atoms, or a hydrogen atom from one of the hydroxy groups of the catechol, or the hydroxyl group of the carboxyl moiety by a covalent bond to Y^a or Y^b

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FIG. 6

Catechol Protection Strategies Applicable for L-Dopa Bile Acid Conjugates

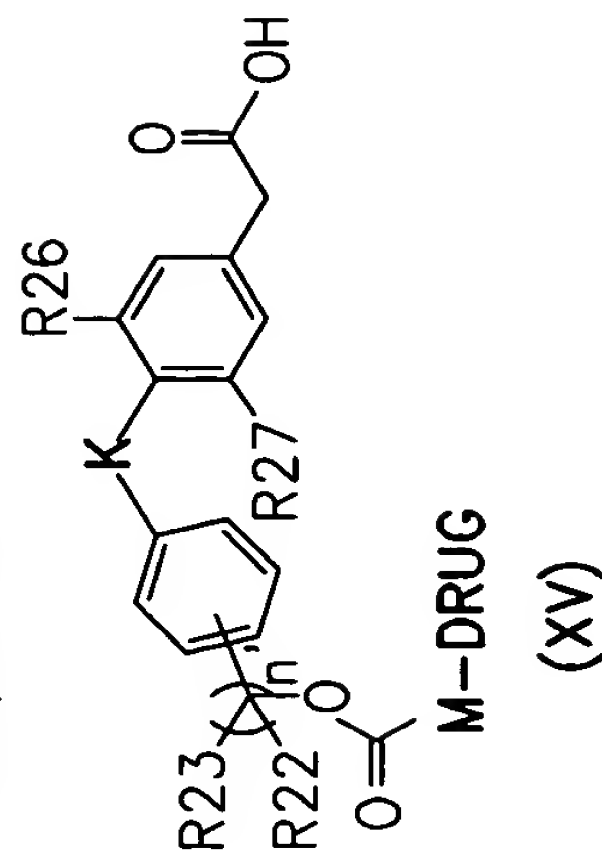
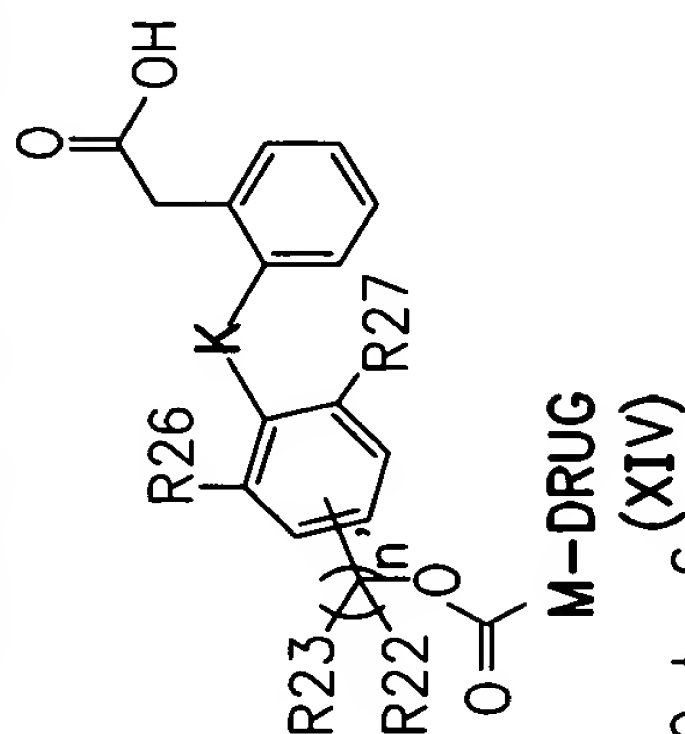


R30 = hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl

R31 = alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl

R24, R25 = hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, substituted heteroaryl or R24 and R25 together with the carbon to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocycloalkyl or substituted heterocycloalkyl ring

Prodrugs For Enterohepatic Circulation via Intestinal and Liver Anion Transporters



$M = 0$, NR7, CR8R9 m' is 0 to 6 ; n' is 0 to 6

$$L = CR8, N$$
$$K = 0, NR7, CR8R9; S(0)_j, j=0, 1, \text{ or } 2$$

Each of R21 to R23 is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, acyl, substituted acyl, acylamino, substituted acylamino, alkylsulfinyl, substituted alkylsulfinyl, alkylsulfonyl, substituted alkylsulfonyl, alkylthio, substituted alkylthio, alkoxycarbonyl, substituted alkylthio, aryl, substituted aryl, arylalkyl, substituted arylalkyl, aryloxy, substituted aryloxy, carbamoyl, substituted carbamoyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, halo, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyloxy, substituted heteroalkyloxy, heteroaryloxy and substituted heteroaryloxy

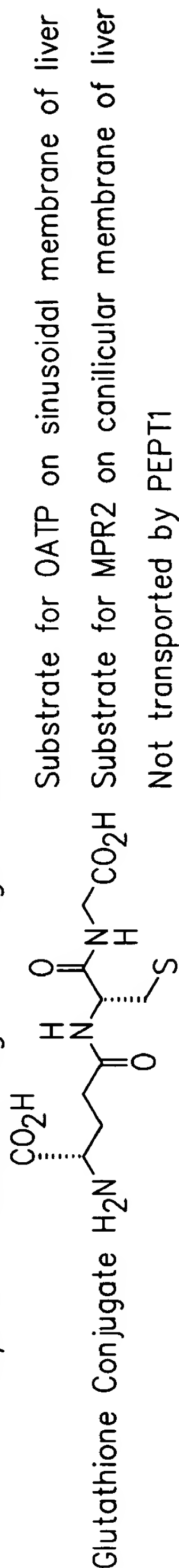
Preferably R22 and R23 are independently selected from the group consisting of hydrogen, alkyl and substituted alkyl

R26 and R27 are independently selected from the group consisting of halo and lower alkyl (including branched alkyl)

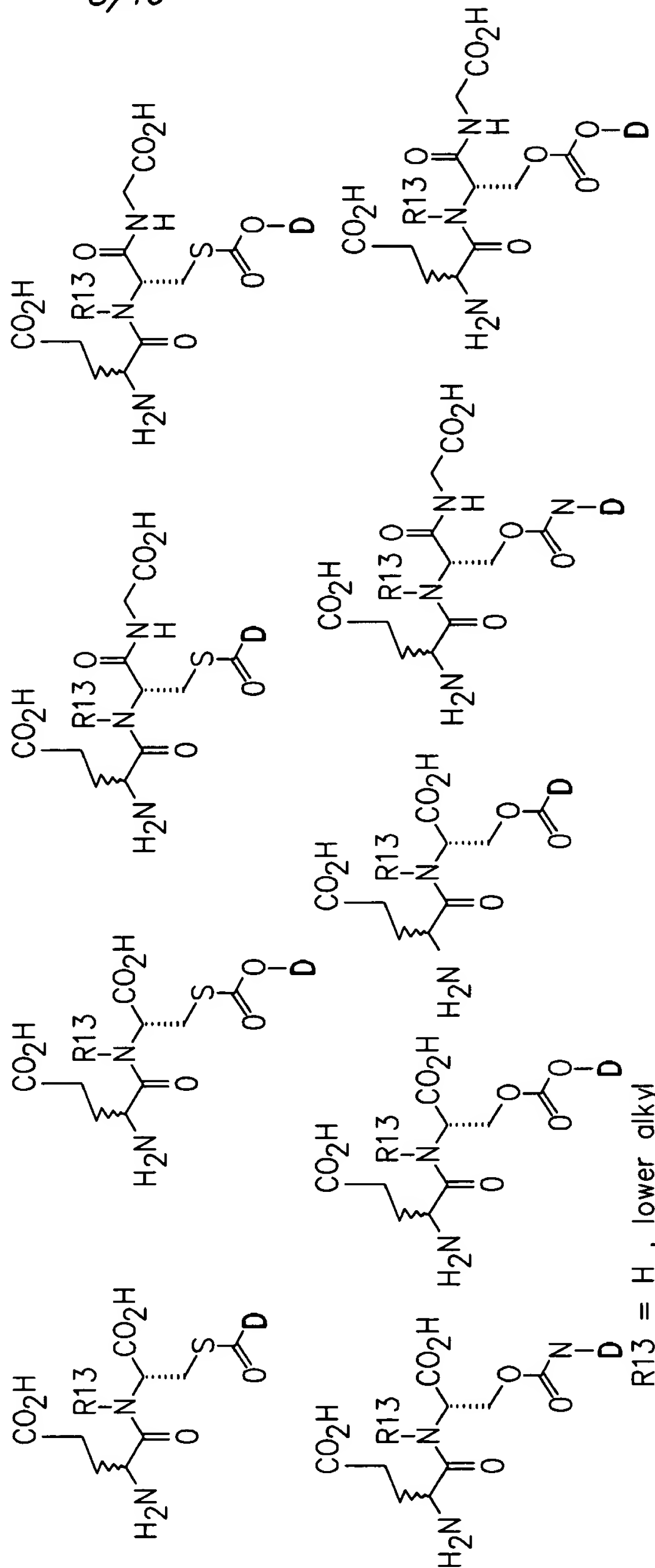
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FIG. 9

Enterohepatic Recirculating Prodrugs Based On Glutathione Mimetics



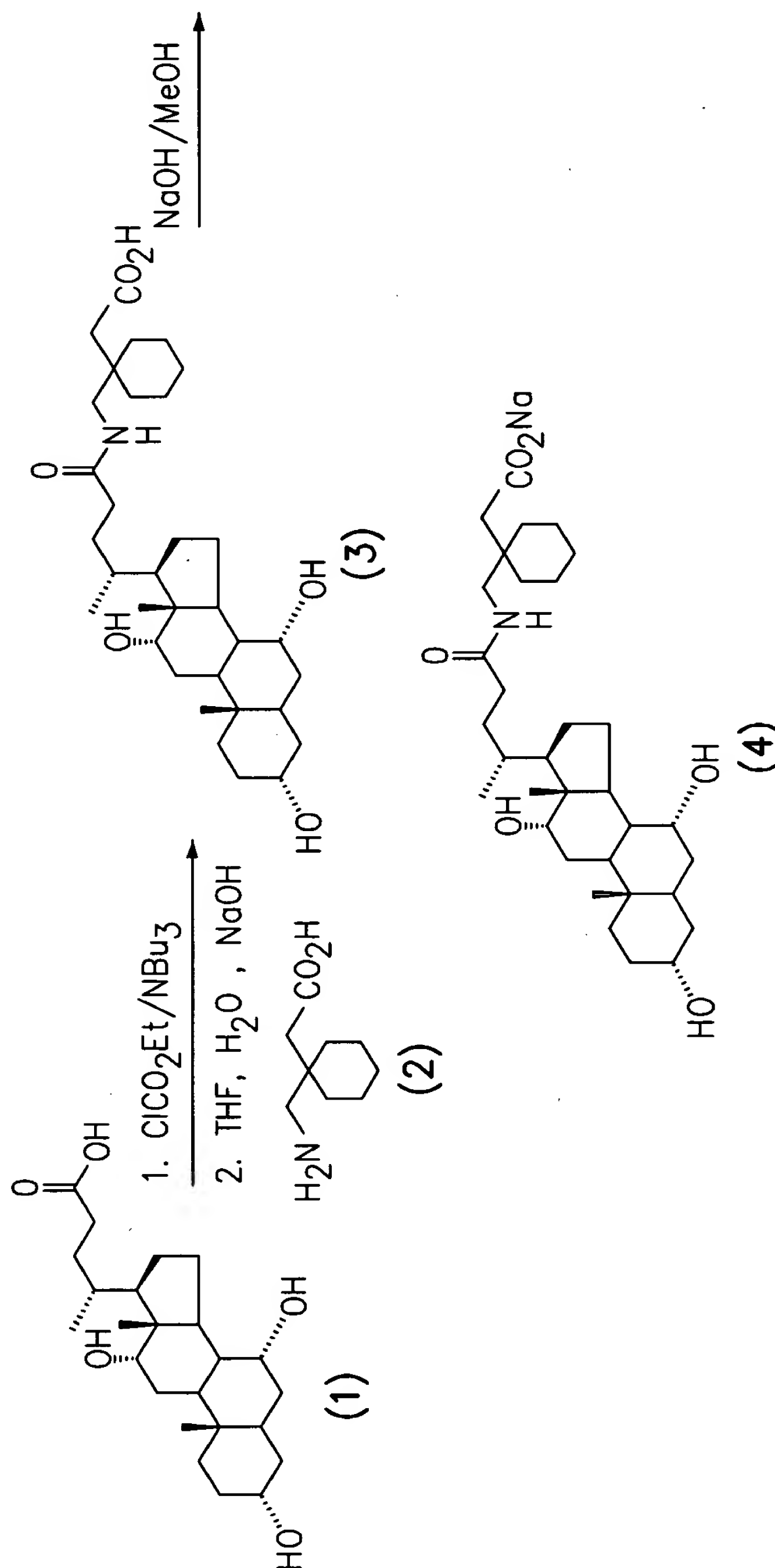
Examples of Di- and Tripeptide Prodrugs of Hydroxyl, Amine and Carboxylic Acid-Containing Drugs Based on Glutathione-Like Motif



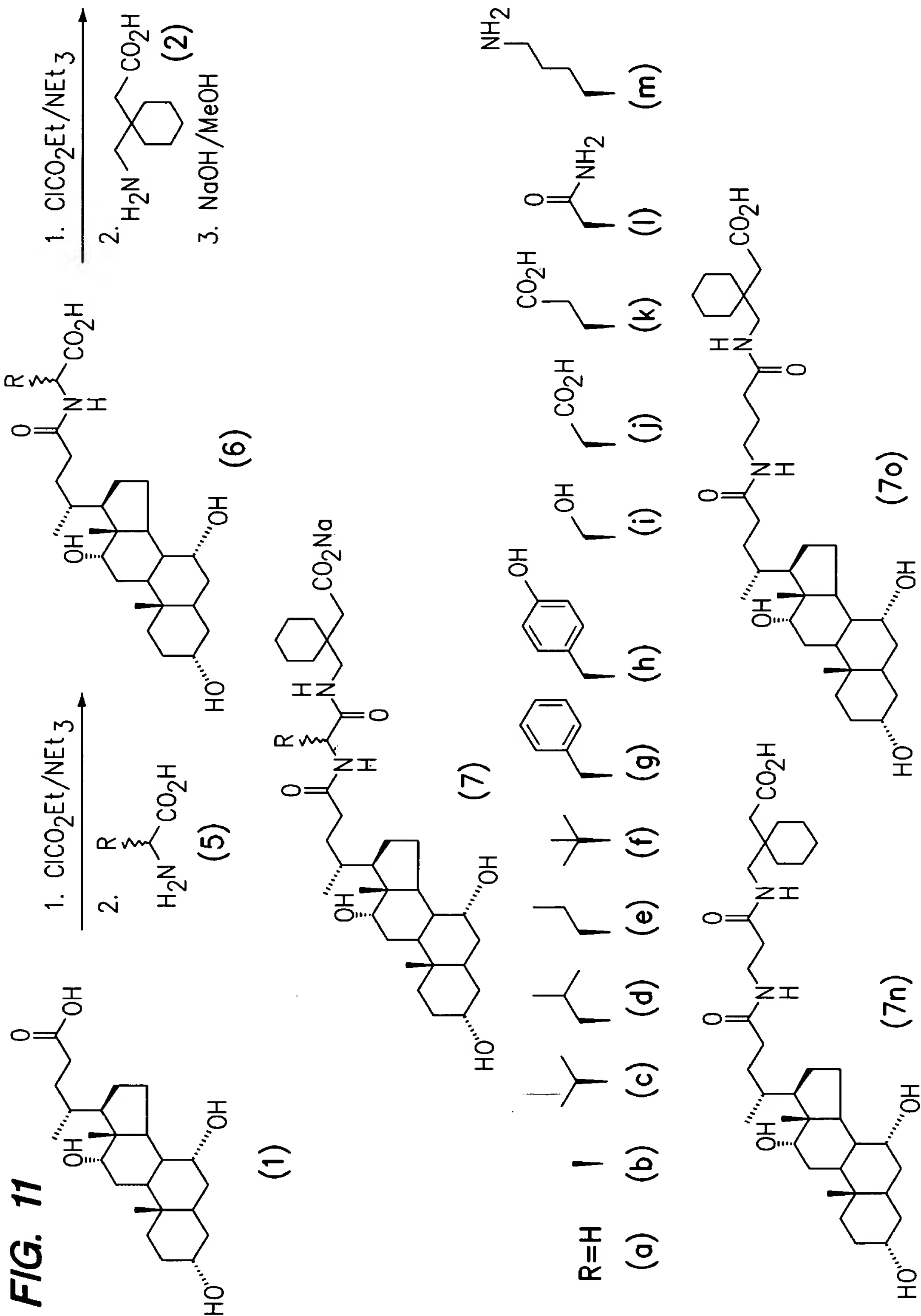
Use PEPT1 substrate with metabolically stable di- or tripeptide backbone to achieve intestinal absorption

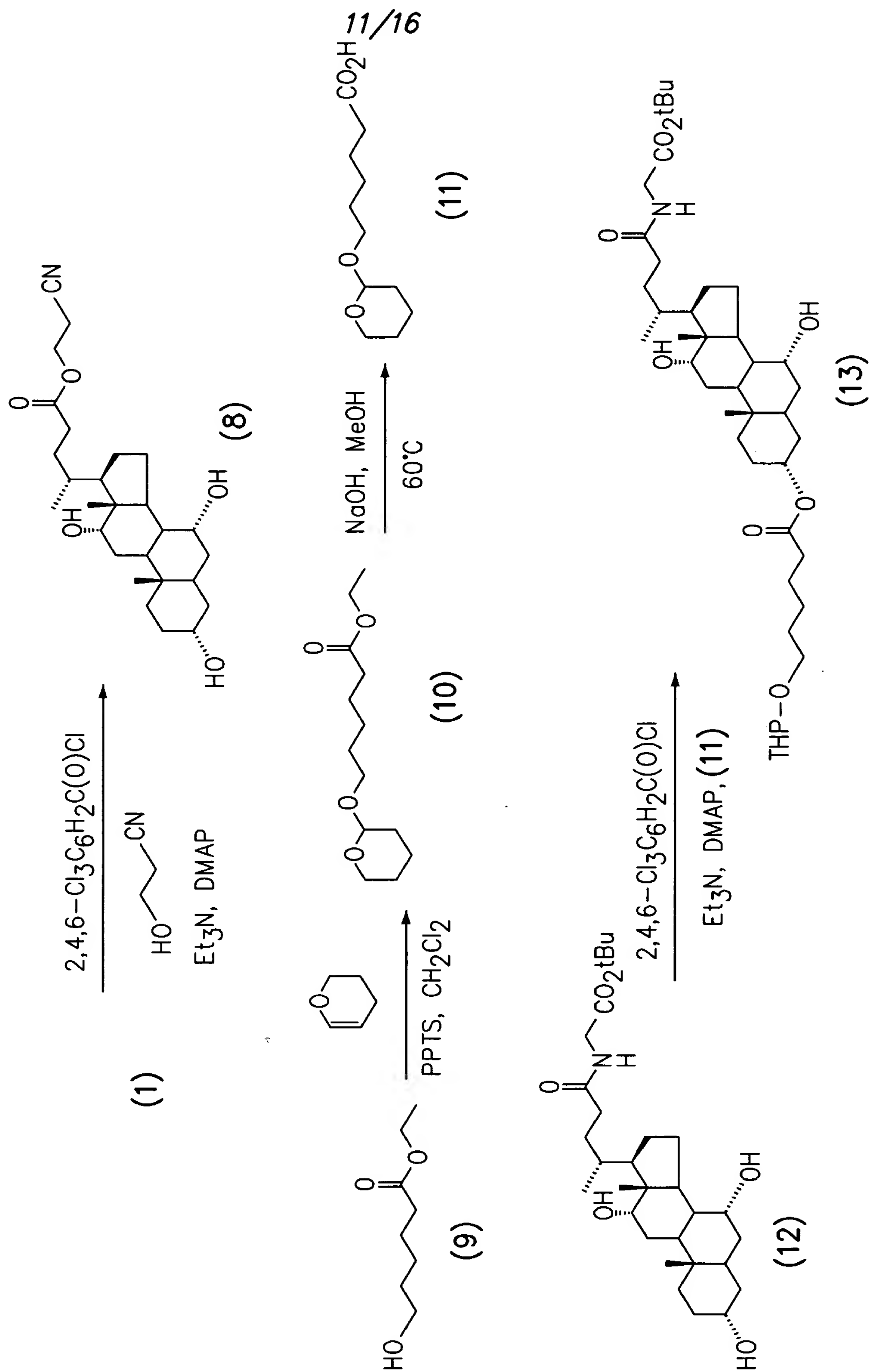
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FIG. 10



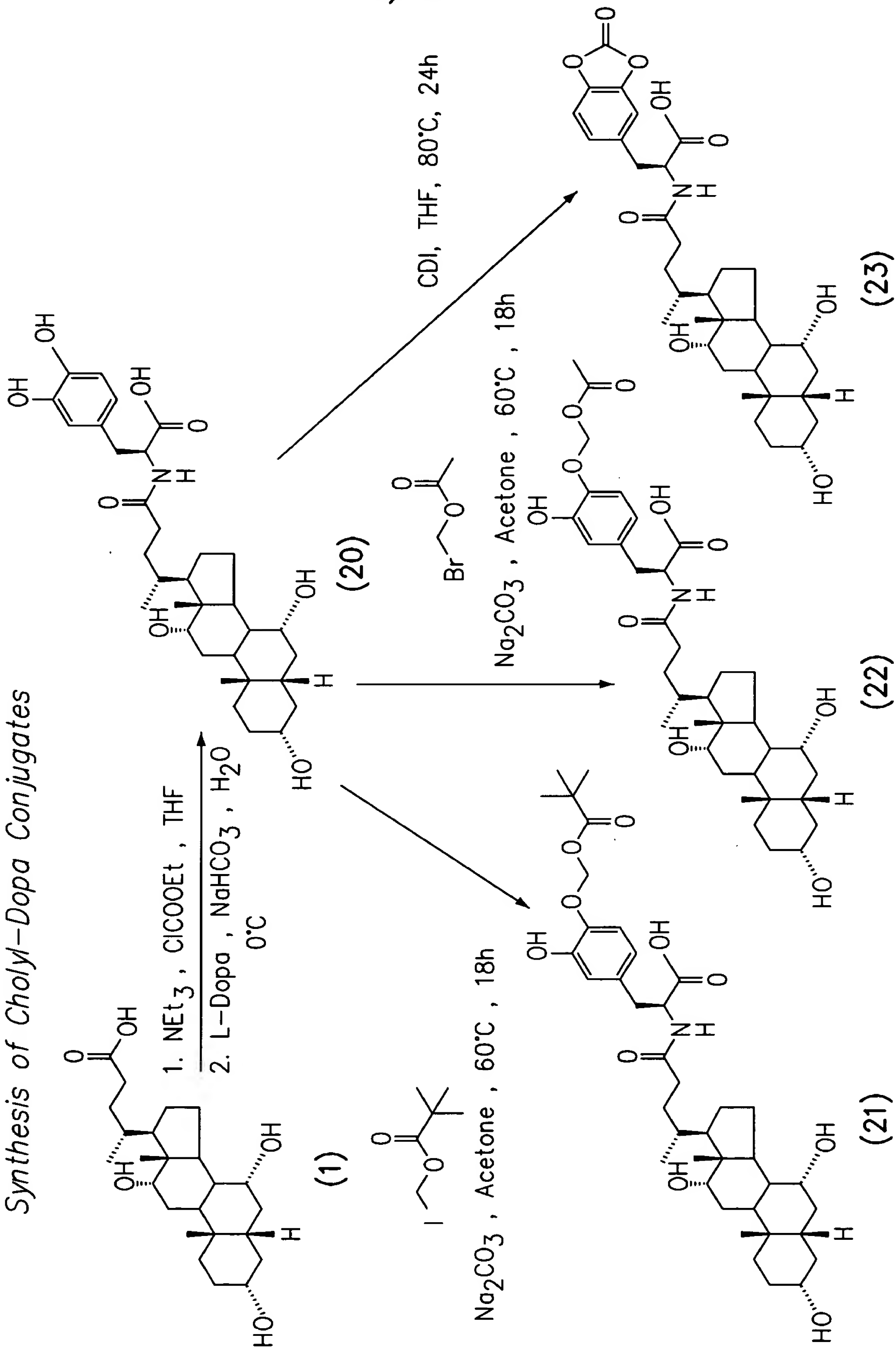
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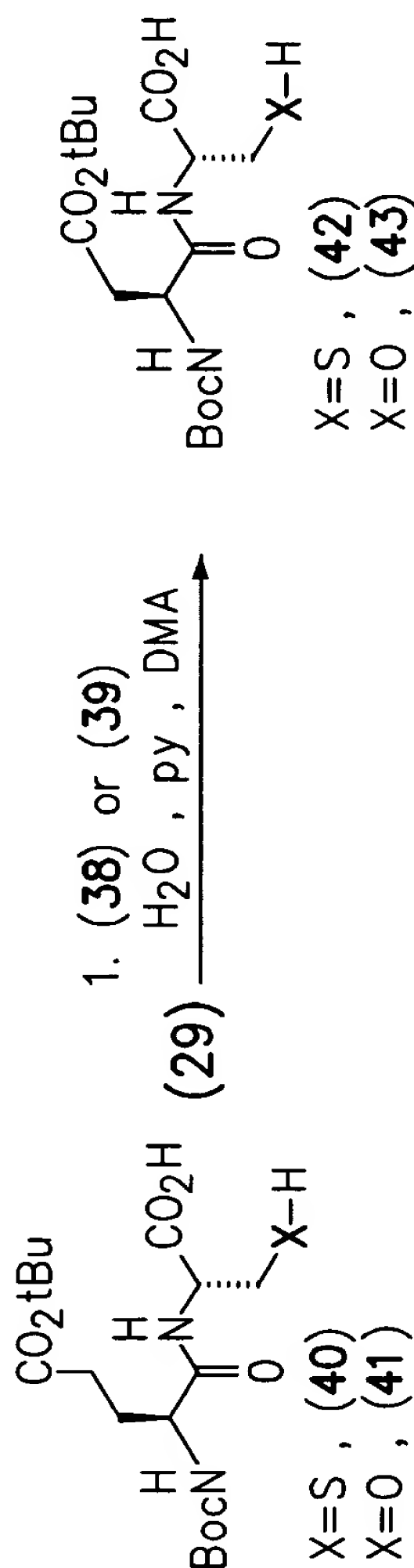
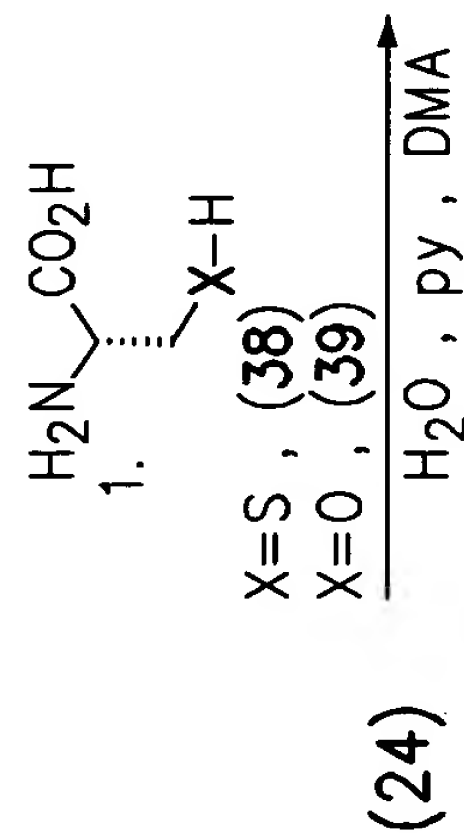
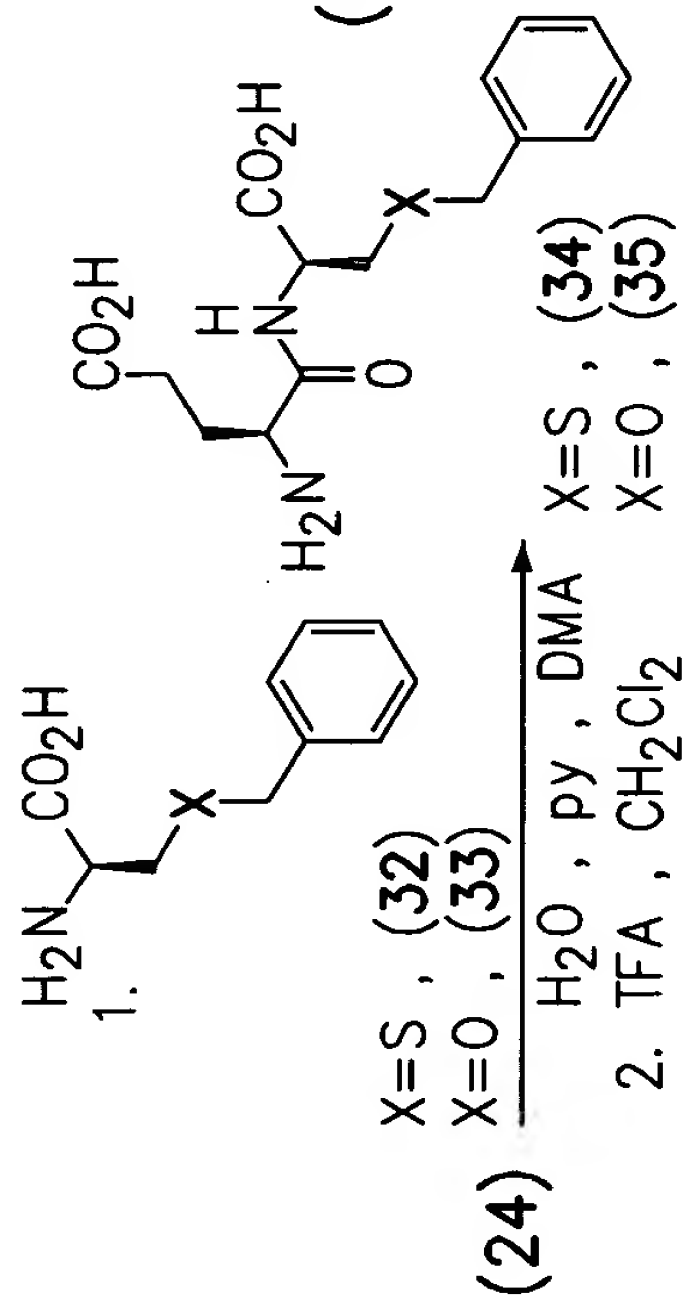
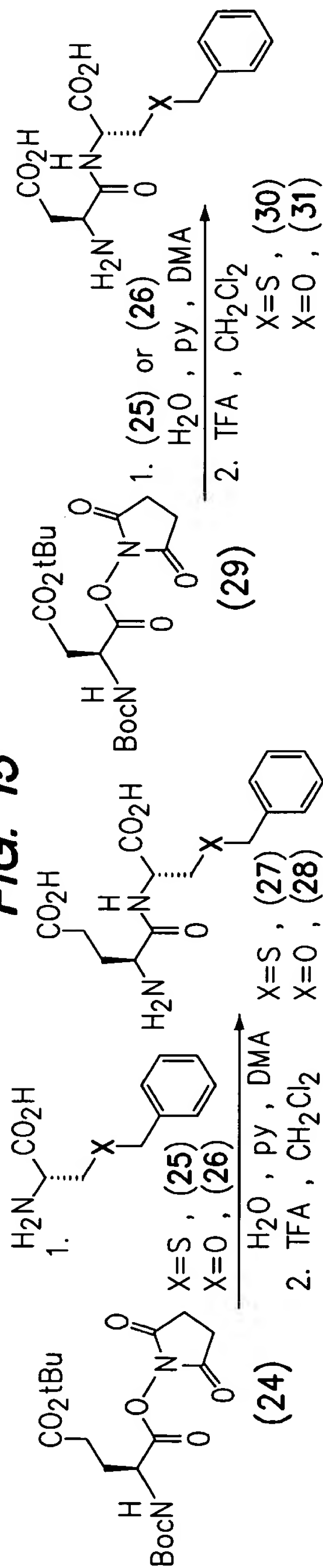
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FIG. 14
 Synthesis of Cholyl-Dopa Conjugates



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FIG. 15



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FIG. 16

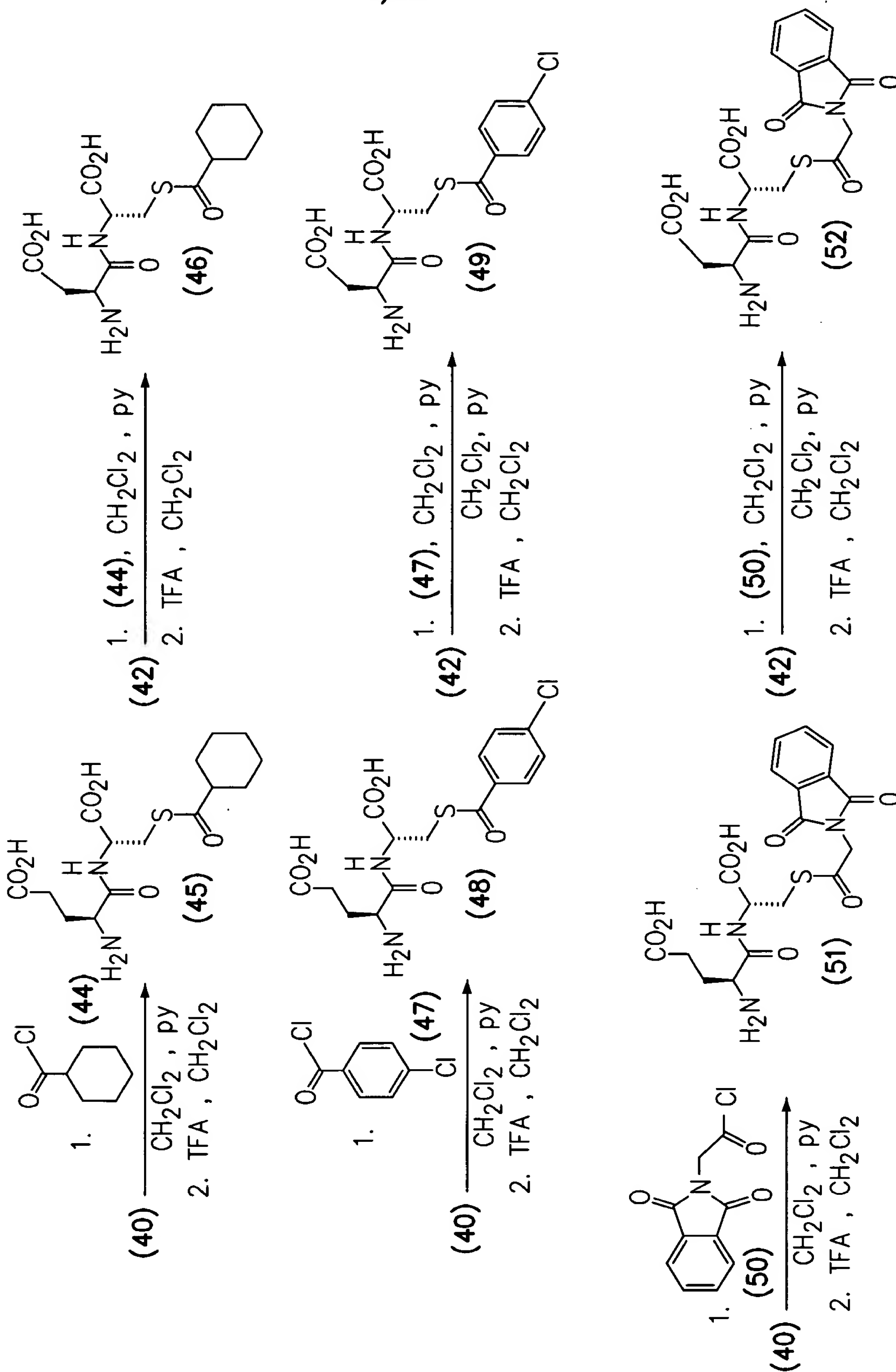


FIG. 17

